DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File for Octapharma BLA 125416/0, pooled plasma (human), solvent detergent (S/D) treated

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Subject: DMPQ Review Memo (BLA): [Octapharma Pharmazeutika, GmbH, U.S. License No.1646]. Original BLA to support market clearance in the US for pooled plasma (human), solvent detergent (S/D) treated with a prion removal process, manufactured at their Vienna, Austria (OPG) and Stockholm, Sweden (OAB) locations.

Action Due Date: 21 – January - 2013

RECOMMENDED ACTION

Recommend approval of Octapharma Pharmazeutika Produktionsges.m.b.H. BLA for Octaplas, pooled plasma (human), solvent detergent (S/D) treated with a prion removal process, manufactured at their Vienna, Austria and Stockholm, Sweden locations.

SUMMARY

Octapharma Pharmazeutika, GmbH (Octapharma) submitted an original biologics license application (BLA), STN 125416/0 on December 22, 2011 to support market clearance in the US for OctaplasLG™, pooled plasma (human), solvent detergent (S/D) treated with a prion removal process, manufactured at their Vienna, Austria (OPG) and Stockholm, Sweden (OAB) locations. OctaplasLG™ is second generation, blood group-specific, solvent/detergent (SD) treated coagulation active plasma for infusion. OctaplasLG™ is prepared using either source or recovered plasma collected in the U.S. The proposed indications for OctaplasLG™ are for management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors, and substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura - TTP). The product is labeled to contain per bag 200 mL of plasma. Manufacturing includes plasma storage to labeling and packaging of final product. CBER Pre-Approval Inspections of the two Octapharma facilities were performed.

The scope of this review includes all of the product manufacturing and facility related information in the original BLA dated December 22, 2011, and amendments submitted. The product and stability data in this submission are under separate review by the product office.

Please note the proprietary name of the product has been finalized on October 5, 2012 as "Octaplas™" to replace the original proposed "OctaplasLG™". The existing non-US S/D plasma is referred as "Octaplas®" or "Octaplas" in the memo, while "OctaplasLG™" is the same as "Octaplas™", and OctaplasLG® is for non-US OctaplasLG.

REVIEW NARITIVES

The review included:

- Module 1: Administrative Information & Product Labeling
- Module 2: CTD Quality Overall Summaries
- Module 3: Quality, 3.2.S, 3.2.P, 3.2.A, 3.2.R
- Amendment #001, STN 125416/0.1, dated 6 Apr 2012
  Response to Telecon of 27-Mar-2012
- Amendment #002, STN 125416/0.2, dated 15 May 2012
  Response to IR of April 25, 2012
- Amendment #003, STN 125416/0.3, dated 24 May 2012
  Response to IR of April 25, 2012
- Amendment #011, STN 125416/0.11, dated 13 Aug 2012
  Product transport protocol PQ and shipment PQ reports [3.2.P]
- Amendment #024, STN 125416/0.24, dated 24 Sep 2012
  Response to 483s for OAB and OPG
- Amendment #027, STN 125416/0.27, dated 9 Oct 2012
  PMC for shipping study

BACKGROUND

Octapharma Pharmazeutika, GmbH (Octapharma) has submitted an original biologics license application (BLA), STN 125416/0 on December 22, 2011 to support market clearance in the US for OctaplasLG™, pooled plasma (human), solvent detergent (S/D) treated with a prion removal process. OctaplasLG™ was developed for US market under IND 13956, submitted on 18 February 2009. It is a modified version of Octaplas®, marketed in Europe since 1992, OctaplasLG™ manufacturing incorporated two significant changes to the process for Octaplas®: (1) reduction of S/D treatment time from 4 – 4.5 hr. to 1 – 1.5 hr. and (2) addition of an affinity column designed to remove prion protein, PrP^{Sc}, the causative agent in Creutzfeld Jakob Disease (CJD). OctaplasLG™ has been approved in several European countries and Australia with its first approval in Germany, in January 2009. If approved, OctaplasLG™ will be the first S/D treated pooled human plasma product on the US market.

PRODUCT DESCRIPTION

OctaplasLG™ is a frozen, sterile, pyrogen-free, solvent/detergent treated (1% tri-n-butyl phosphate/ 1% octoxynol), pooled human plasma product filled in 200 mL doses into 300 mL PVC plasma bags. Each batch is manufactured from pooled plasma of 390kg composed of 630 to 1,520 single donor units of either Source Plasma or recovered plasma from the same ABO blood group. OctaplasLG® is indicated for management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors, and substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura - TTP).

MANUFACTURERS [MODULE 3.2.S.2.1]

OctaplasLG™ will be manufactured at the following two locations under U.S. License No.1646:

1. Octapharma AB, (OAB)
   Elersvagen 40, SE - 112 75,
   Stockholm, Sweden
   FEI: 3005559915

2. Octapharma Pharmazeutika Produktionsges.m.b.H, (OPG)
   Oberlaaer Strasse 235, 1100
   Vienna, Austria
   FEI: 3002809097

CBER performed Pre-License Inspections of the two Octapharma facilities to support this application resulting in 10 inspectional observations issued for Octapharma OAB on July 30, 2012, and 7 inspectional observations issued to Octapharma OPG on August 7, 2012 which are documented in the Establishment Inspection Reports. The PLI was the first FDA inspection for the production lines and the areas used for manufacturing OctaplasLG™ (US) at OPG and OAB. Please refer to EIR and 483 response review memo for inspection related issues.

FACILITIES

OctaplasLG™ production areas in the two manufacturing facilities are also shared with other products as listed in the table below:

Production facility	**Product sharing same production area with OctaplasLG™ US**
Octapharma AB, (OAB) Elersvagen 40, SE - 112 75, Stockholm, Sweden FEI: 3005559915	• ---------(b)(4)---------- • ---(b)(4)--- • ---(b)(4)--- • ---(b)(4)--- ---------- (b)(4)----------

Production facility	**Product sharing same production area with OctaplasLG™ US**
Octapharma Pharmazeutika Produktionsges.m.b.H, (OPG) Oberlaaer Strasse 235, 1100 Vienna, Austria FEI: 3002809097	• ---------(b)(4)--------- • ---(b)(4)---

OctaplasLG production areas at both OAB and OPG are all divided into --------(b)(4)---------- Aseptic production, and ----(b)(4)---- packaging areas. The (b)(4) area comprises a bulk area where the following operations are performed: thawing and pooling, ---(b)(4)---, filtration, ------(b)(4)-------, preparation and addition of S/D reagents and chemicals. The (b)(4) area also includes -------(b)(4)-------. The (b)(4) area comprises a bulk area where the following operations are performed: ------(b)(4)-------, filtration, removal of S/D chemicals via phase separation and C-18 cartridge, Prion reduction, ----------(b)(4)---------- transfer to filling, ----------(b)(4)----------. The --(b)(4)-- area also includes ----------(b)(4)----------. The Aseptic production area includes sterile filtration and filling. Packaging area includes visual inspection, packaging into single cartons and fast freezing in ----------(b)(4)----------, visual inspection of frozen bags and packaging into transport cartons.

OAB production facilities are located in Building (b)(4) on the (b)(4) floor. Plasma storage rooms are located in Building --------(b)(4)------ floor. The (b)(4) floor of Building ---(b)(4)--- houses the Main Storage for raw materials. The Quality Control laboratories are located in Building (b)(4). The Administrative functions are located in Building -----(b)(4)-----. The Stability rooms are located in Building (b)(4).

Other products manufactured at **OAB** facility but not sharing the same production area with OctaplasLG™ include:

- Octanate®, purified factor VIII concentrate
- Nanotiv®, high purity factor IX concentrate
- Albumin/Albuminativ®, human serum albumin 4%, 5 %, 20% and 25%
- Atenativ®, high purity antithrombin III concentrate
- Gammanorm®, immunoglobulin for intramuscular or subcutaneous use
- Octagam®, immunoglobulin for intravenous us
- Rhesonativ®, immunoglobulin anti-D

----------(b)(4)----------. Only sterile products in liquid dosage forms and aseptically prepared products are produced at this site.

Octaplas® and OctaplasLG™ are not manufactured in the same area as the rest of the above mentioned products.

OAB warehouses:

1) ----------(b)(4)----------
---(b)(4)--- handles storage and sampling of components. ----(b)(4)---- also handles storage, sampling and dispensing of raw materials.

2) Octapharma AB, Elersvägen 40, SE-112 75 Stockholm, Sweden
Freezers in building (b)(4) is used for storage of -------(b)(4)------- finished packed goods.

OPG production facilities for OctaplasLG™ are located in Building (b)(4). Plasma storage rooms are located in Building (b)(4). Building (b)(4) houses the Main Storage for raw materials. The Quality Control laboratories are located in Building (b)(4). The Administrative functions are located in Building ---(b)(4)---. The Stability rooms are located in Building (b)(4).

Other products manufactured at **OPG** facility but not sharing the same production area with OctaplasLG™ include:

- Octanate® (purified factor VIII concentrate)
- ----------(b)(4)----------
- Albumin/Albuminativ® (human serum albumin 4%, 5 %, 20% and 25%)
- ----------(b)(4)----------
- ----------(b)(4)----------
- Octagam® (immunoglobulin for intravenous use)
- ----------(b)(4)----------
- Octaplas® (S/D-treated blood group specific Human Plasma)
- ----------(b)(4)----------
- ----------(b)(4)----------
- Octanine F ----------(b)(4)----------

OPG warehouse besides on site facility:

1) ----------*(b)(4)*----------
----------(b)(4)----------

- ----------(b)(4)----------
- ----------(b)(4)----------

Testing Facilities Shared for Both Sites:

Octapharma uses (b)(4) contract analytical laboratories to support the quality control of OctplasLG, and samples from both OAB and OPG are tested by these facilities:

(1) ----------(b)(4)----------:

- ----------(b)(4)----------

(2) ----------(b)(4)----------

- ----------(b)(4)----------

This submission provides detailed descriptions of the construction of the rooms, floor diagrams with room numbers, and directional flow arrows for Buildings that indicate the usage of the facilities for manufacture of OctaplasLG™, including: Product and raw materials; Personnel; Equipment; Waste; and Air. Octapharama stated that OctaplasLG™ production lines are only shared by EU and US OctaplasLG. The initial submission does not contain sufficient information regarding sharing of the production rooms and equipment with other products also produced in the same facilities. Octapharma has submitted amendment #1, #2 and #3 to address our IR questions 1 and 2 from our March 7, 2012 Telecon and April 25, 2012 IR letter regarding these issues.

MANUFACTURING PROCESS [Module 3.2.P.3.3]
Octapharma states that the starting batch size for both sites is 390kg from either recovered or source plasma, and manufacture of OctaplasLG™ consists of (b)(4) manufacturing steps as outlined below:

(b)(4)

6 PAGES REDACTED (B)(4)

MAJOR EQUIPMENTS [Module 3.2.A.1.3]

OAB site

The production line at OAB is newly installed and validated in 2011. Equipments at OAB are qualified to process 390 kg --(b)(4)-- starting amount of plasma, although only 390kg batch is submitted in the BLA. The major equipment used for the manufacture of OctaplasLG™ at OAB is listed in the following table together with the location and identification number, a brief description and at which step in the process they are used. All equipment, except for the ----------(b)(4)----------. Only US sourced plasma are used for US Octaplas, and non US sourced plasma are used for non US Octaplas manufacturing.

(b)(4)

(b)(4)

OPG site:
OPG is routinely manufacturing *Octaplas* since 1992 and octaplasLG since 2009. . The major equipment used for the manufacture of octaplasLG at OPG is listed in the following table together with the location and at which step in the process they are used. All equipment, except ----------(b)(4)----------.

(b)(4)

(b)(4)

CLEANING AND SANITIZATION [Module 3.2.A.1]
In amendment #3, Octapharma provided following cleaning validation reports from both OAB and OPG sites:

- Report 080RPQ12202.000: "Summary of Validation Reports concerning Cleaning /Sanitation / Sterilization / Depyrogenisation for equipment used during Octaplas LG processing", (**Doc.No.:** 080RPQ12202.000).
- Report OC12-0157: "Summary of Validation Reports concerning Cleaning and Sanitization of Stainless Steel Vessels used in the OctaplasLG Production at Octapharma AB, Stockholm

The report summarizes both automatic and manual cleaning results of the validations concerning cleaning (including the hold time studies), sanitization / sterilization and depyrogenation for each equipment item related to the OctaplasLG™ processing.

The defined cleaning cycles are designed to assure adequate cleaning by removing ----------(b)(4)------ and the -----(b)(4)-----. The (b)(4) is conducted with ---------(b)(4)----------, ----------(b)(4)----------. At both sites, ----------(b)(4)---------- has been performed in the course of the cleaning validation for (b)(4) of stainless steel vessels.

Testing methods and acceptable criteria are listed in the table below:

(b)(4)

----------(b)(4)----------:

(b)(4)

Automatic Cleaning and Sanitization

Automatic Cleaning and Sanitization procedures are used for equipment e.g. all stainless steel tanks and piping. The equipment in -(b)(4)- area is cleaned by ----------(b)(4)---------- system. The equipment in --(b)(4)-- area is cleaned by ----------(b)(4)----------. The (b)(4) cycle for OPG and OAB is defined as follows:

3 pages redacted (b)(4)

----------(b)(4)----------

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(b)(4)

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----------(b)(4)----------

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CONTAINER CLOSURE SYSTEM [Module 3.2.P.7]:
There are two suppliers for the plasma bags used for OctaplsLG:

Component	Size	Material	Quality Standard	Supplier	Master File
Bag	**300 ml**	**PVC**	**---------- ---------- (b)(4)---------- ----------**	**---------- ---------- ---(b)(4)---------- ---------- ---------- -------**	**---------- ---------- -----(b)(4)---- ---------- ---**

Bag	**300 ml**	**PVC**	**----------(b)(4)----------**	**----------(b)(4)----------**	

In-house specifications 013AMVPBC/10 for plasma bag receipt from ----(b)(4)---- and 013AMVPBF/02 for plasma bag receipt from ----(b)(4)---- were provided in module 3.2.P.7.

300 mL plasma bags are used as primary packaging materials for OctaplasLG and are received sterile (------(b)(4)--------). The specification of the sterile bags was described in the submission. 200ml of the finished OctaplasLG™ product is first filled into sterile polyvinyl-chloride (PVC) bags of standard types used for collection, storage and freezing of blood components as immediate container. The volume capacities of these bags are 300 mL. The quality of the bags conforms to (b)(4) quality standard (see module 3.2.P.3.3, manufacturing procedure 150MOP952/02/US, section 1.2. Auxiliary Materials). The filled and labeled bags are vacuum-sealed by over-wrapping ---------(b)(4)---------- film as outer containers and subsequently frozen. After (b)(4) freezing in the -------(b)(4)------- the bags are packed in cartons of ten and stored at ≤ -18°C and protected from light.

Container Closure Integrity Testing (CCIT) study reports are included in the submission: Container/Closure Integrity testing, Human Plasma S/D treated primary packaging systems, Study no. 04P003, (b)(4) months' data (000SSR992.04P003.01/INT)

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----------(b)(4)-

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Container material qualification is reviewed by product office.

VALIDATION OF ASEPTIC PROCESS AND FILLING LINES [Module 3.2.P.3.5]
The submission contains two qualification reports for aseptic process at OAB and OPG sites respectively, and in amendment #3 response to IR Question #9, Octapharma provided detailed qualification reports for both filling lines.

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4 pages redacted (b)(4)

(b)(4)

----------(b)(4)----------

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During PLI, the filling room and filling line was inspected. EIR excerpt regarding the filling operation at OAB is copied below in *italic:*

Facility Walk-Through
On Tuesday July 24, 2012 the inspection team performed a walk through of Building ----------(b)(4)- floor manufacturing area and observed manufacturing operations. We entered the Packaging Room (b)(4) and a small -----(b)(4)----- Room (b)(4) to observe product filling in the Class (b)(4) Filling Room (b)(4). The Filling Room contained an automated bag filling machine ----------(b)(4)----------. The window in Room (b)(4) allowed viewing of the (b)(4) side of the filling machine. The windows in Room (b)(4) allowed viewing of the ----------(b)(4) ----------and the (b)(4) side of the Filling Room. The filling machine was observed being loaded with empty bags on the (b)(4) end of the filling machine, where the -----(b)(4)------ carries the bags towards the -(b)(4)- side of the machine through various ----------(b)(4)----------. The filled and sealed bags are then conveyed to the ----------(b)(4)----------. Bags outside of the (b)(4) specification are sent to the ---(b)(4)---. Accepted bags are sent to the ---(b)(4)--- Packaging Room where they are (b)(4) sorted onto the packaging machine.

In the Filling Room, Operator (b)(4) was observed removing the empty bags from its sterile packaging and placing the bags onto a loading station on the ---(b)(4)--- end of the filling machine. Operator (b)(4) was observed seated on the --(b)(4)-- side of the Filling Machine attaching the bags onto a ----------(b)(4)---------- operators were observed appropriately gowned for the aseptic operations in the filling room and practicing proper aseptic techniques. Materials were cleaned with -------(b)(4)------ prior to entering the Class (b)(4) region. Operators applied sanitizing agents to their hands before and after handling materials or before entering the Class (b)(4) regions. Movements performed by the operators were deliberate and direct to avoid unnecessary motion that can disturb the uniform air flow in the room and to minimize contact with surfaces.

3. Filling Area
(AL) *Filling is performed in room (b)(4) under aseptic conditions in a grade (b)(4) environment. The product is ----------(b)(4)---------- and then passes through an ----------(b)(4)---------- area of the filling room. The sterile final bulk solution is then filled into 300 mL bags on the filling machine in the grade (b)(4) area. The grade (b)(4) area is protected by a ----------(b)(4)---------- the filling machine. Material entry into the room is through either the ---(b)(4)--- or through the ---------(b)(4)----------. Personnel entry and exit is through a ----(b)(4)----.*

(b)(4) operators were observed in the filling room fully gowned. Operator (b)(4) was observed taking materials from an equipment ---(b)(4)---, removing the outer wrap, and unloading

the 300 mL sterile bags into one side of the bag loading station of the filling machine. Operator (b)(4) was observed seated on the other side of the bag loading station placing the 300 mL bags onto the filling machines ----(b)(4)----. Bags are ----------(b)(4)----------. The (b)(4) operators were observed using proper aseptic technique such as using slow and deliberate motion, spraying hands with sanitizers before entering the grade (b)(4) area, careful handling of the sterile bags and by minimizing unnecessary contact with surfaces.

The filling machine is an automated unit with operators manually loading the closed and empty sterile bags onto the bag -----(b)(4)----- on one end of the machine. The bags are then ----------(b)(4)----------. The bags are then dropped onto a ----(b)(4)---- and transported to a class (b)(4) area room ----------(b)(4)----------. Bags failing the ----(b)(4)---- are automatically ---(b)(4)--- and sent to a ---(b)(4)---. The accepted bags are then transported through a (b)(4) into the ---(b)(4)--- Labeling Packaging Area.

In the **OPG** site, the aseptic filling line "---(b)(4)----------" of OCTAPHARMA Vienna is used for the production of ----------(b)(4)----------. The report titled “Qualification of the aseptic filling line Production Octapls” (Doc.No.: 060RPQ001-18 media fill Octaplas 2011 Q3.doc), validation of the Octaplas filling line “----------(b)(4)----------” was performed by media fills in a requalification study conducted in 2011 according to 001 SOP509. (b)(4) batches with a total of (b)(4) units were tested on the ----------(b)(4)---------- filling line without a single failure.

The key data of the media fill with Octaplas are listed in the tables below:

(b)(4)

---------(b)(4)----------:

(b)(4)

----------(b)(4)----------:

(b)(4)

----------(b)(4)----------

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Historical data from -(b)(4)-- units produced on the same filling line without any contamination since 2002 were also included to show the consistent quality of the filling line system. From these data, the ----------(b)(4)---------- for the aseptic filling line "----------(b)(4)---------" could be demonstrated, as recommended by ---------(b)(4)--------- for aseptic processing. The filling line is requalified every ----(b)(4)----.

Packaging and Labeling System

Packaging and labeling system was inspected during PLI. EIR excerpt regarding the system is copied below in italic:

For OAB site:

4. Labeling, Packaging, Visual Inspection and Freezing

(AL, JH, NK) *Labeling, packaging, visual inspection and freezing operations are performed according to SOP 6001-OP: Visual Inspection, Packaging and Freezing [Ex. NK-4], immediately following filling operations. On 24 July 2012, the inspection team (AL, JH, NK) observed labeling, packaging, visual inspection and fast freezing operations for Lot ----(b)(4)----. Octapharma personnel, Kicki Garheden Fredriksson, Christina Leo,*

Katrin Karlsson, ----------(b)(6)---------- explained the process and answered questions.

The filling area is adjacent to the packaging area. After filling, plasma filled bags are ---(b)(4)--- in a Grade ---(b)(4)--- room. The ---(b)(4)--- bags are then passed into the packaging area. In the packaging area, a label is placed onto each bag using an automated process; each labeled bag is overwrapped and then vacuum sealed. Visual inspection is performed on labeled, overwrapped, vacuum sealed product. There is no visual inspection through the inner bag before labeling and overwrap. Visual inspection is performed on ----------(b)(4)----------. Bags with observed defects, such as missed or damaged labels, leakage, or foreign objects, are removed and placed into a designated, ---(b)(4)--- stored on the floor. We (AL, JH, NK) observed rejected bags in a ---(b)(4)--- marked föroreningar (foreign particle). It was explained that foreign particles occurring between the inner bag and overwrap were the most common visual defect. Such bags may be ----------(b)(4)---------- operations. Product that passes visual inspection is packaged into a carton with the label placed toward the window. Packaged product is placed onto a ----------(b)(4)----------, located in the packaging area. Freezing is a (b)(4) process comprising ----------(b)(4)----------..

During observation of the visual inspection process, the inspection team observed no in-process tallying of individual, identified visual defects. (Refer to 483 Observation #7).

For OPG site:

(AL) *The packaging area room --(b)(4)-- is a controlled ---(b)(4)--- area. The sterile filled 300 mL bags are loaded onto the labeling packaging machine, where labels are applied to the primary container. The labeled bag is then vacuum sealed with an outer wrapping and visually inspected for proper labeling and bag integrity. The labeled bags are then fast frozen in a --------(b)(4)--------- and then visually inspected for damages.*

Labeling and secondary packaging is performed by an automated machine. The filled 300 mL bags are manually loaded by operators onto the -----(b)(4)---- with -------(b)(4)------ feeding into the labeling machine. Labels are applied by the machine and the bags are then vacuum sealed into a secondary container. (b)(4) cut the secondary container apart into individual blister packs with a single labeled 300 mL bag within. The bags are visually inspected for labeling and packaging defects by (b)(4) operators. Defective bags are removed and placed into ----(b)(4)---- for separating the defect types, such as missed or damaged labels, improper sealing or bags containing foreign objects.

The accepted bags are then packed into single cardboard cartons and loaded onto -------(b)(4)-- racks for the freezing process. Filled (b)(4) are then loaded into ----------(b)(4)---------- fast freezers. Approximately ---(b)(4)--- in the freezers achieves the maximum

target temperature of -------(b)(4)------ temperature of the filled bag. Bags are then removed from the fast freezer and visually inspected for damage. Defective bags are rejected and accepted bags are stored in a (b)(4) freezer until final testing and release are completed.

C-18 COLUMN [Module 3.2.P.3.5]
C-18 column chromatographic is used in Step 4 of the production process to remove Octoxynol and residual TNBP from the ----------
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  ----------(b)(4)----------

- ----------(b)(4)----------
- ----------(b)(4)----------

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----------(b)(4)----------

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Testing results show each evaluated parameter met the corresponding acceptance criterion. Based on the results of final rinse, sufficient cleaning of the C-18 chromatography columns with the cleaning process used can be stated.

The cleaning and regeneration results for all the (b)(4) conformance lots met the acceptance criteria for all tested parameters

Revalidation of the cleaning process is performed ----------(b)(4)----------

Review comments:
This column and resin are dedicated to US plasma, and the same resin material is designed to be used for (b)(4) batches. A validation report is included demonstrating the column maybe used for at least ---------(b)(4)---------- (Section 3.2.P.5.5). But the cleaning and regeneration uses ---(b)(4)---, and the cleaning acceptance includes only ----------(b)(4)---------- testing. There is no information on accessory parts, such as gaskets and tubing connectors, for their cleaning and replacement intervals. These issues were discussed during PLI, and Octapharma agreed to use dedicated resin and column for US OctaplasLG™ production.

EIR excerpt regarding the column is copied below in italic:

> *2. Chromatography Columns*
> ***(JH)*** *There are two chromatography columns utilized in the OctaplasLG manufacturing process, including C18 column used in Step 4 and LG column at Step 6. The C-18 column is used as solid phase to extract any remaining S/D reagent (Octoxynol) after S/D treatment from the flow through plasma pool. The LG (Ligand Gel) column is used for reducing prion protein from the S/D treated plasma pool.*
>
> *I interviewed ----(b)(6)-----, Katrin Karlsson, Kicki Garheden Fredriksson and ---(b)(6)----- regarding the (b)(4) column during the inspection. The firm provided the following documents regarding the two columns:*
> - *SOP 6003-OP Version 2 for C-18 column preparation and operation;*
> - *C-18 life cycle validation study report, [FOC 101 HC 0401 – FOC 101 HC 0407];*
> - *SOP 6004-OP Version 1 for LG (prion) column preparation and operation;*

- *---(b)(4)--- validation of C-18 chromatography in the OctaplasLG productionprocess as used for column validation studies*
- *Final report of the installation and operational qualification of the chromatography columns and devices. (Part of the IR response as amendment #3)*

The inspection was concentrated on the (b)(4) column, since this is a column validated for (b)(4) uses, and the (b)(4) column is -----(b)(4)-----. Currently, there is ----(b)(4)----- column used for OctaplasLG production, and the column is ----------(b)(4)---------- column unit consists of the following:

- ----------(b)(4)----------
- *-----(b)(4)------*
- *---(b)(4)---*
- *----------(b)(4)----------*
- *----------(b)(4)----------*

----------(b)(4)----------:

(b)(4)

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----------(b)(4)----------

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----------*(b)(4)*----------
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PRION REMOVAL LG COLUMN [Module 3.2.P.3.4 and 3.2.P.5]
----------(b)(4)---------- developed the ----(b)(4)---- affinity resin for the capture and removal of prion. Octapharma uses this resin in step 6 of the manufacturing process to remove potential prion proteins from the S/D treated plasma. This resin is ---(b)(4)---. In the submission Octapharma provided data for the resin qualification, validation including leachable study, and cleaning validation.

- **Affinity ligand gel (LG) column**. A report investigating possible leachables from column material is enclosed in Section 3.2.P.5.5. Characterisation of Impurities: "Leachate Analysis Results for Samples Supplied as part of Sample Analysis Proposal dated August 2011".
- ---(b)(4)--- study report: ----------**(b)(4)**---------- **Safety, Leachables and Extractables**. 05-Jul-20102
- According to SOPs 087SOP004, 087SOP006 and Change Control CC 08/050 **Cleaning Validation Equipment family "---(b)(4)--- Octaplas" Prion Columns** [FOC 101 HC 0302 – 0307] Production 2

---(b)(4)--- is the vendor for LG resin, and conducted the leachate analysis study. (b)(4) OctaplasLG™ samples were tested by (b)(4) with the method described in report 138/R22/8/091207, and no significant leachates in any of the samples analyzed.

LG column cleaning was Validation was performed according to SOPs 087SOP004 and 087SOP006 at OPG. ----------
----

----------(b)(4)----------

----------. Results from (b)(4) runs met cleaning acceptance criteria, and no deviation occurred.

Firm stated in addition to the ---(b)(4)--- columns, ---(b)(4)--- columns may also be used but no information was submitted. The resin and column are ----------
--(b)(4)----------.

Revalidation of the cleaning process will be carried out when ----------
-----(b)(4)---------- following a review.

Resin for this step is ---(b)(4)---, but the firm has not stated clearly if the column is shared with non US OctaplasLG. Column specification, materials composition, accessory parts, cleaning protocol, validation study and details of column running condition are not provided in the submission. The submission does not contain information on the chromatography -------(b)(4)---- used with this column. Additional follow up information was provided in amendment #3 for IR question #5 and #7.

---(B)(4)--- FREEZER

In step (b)(4) of the manufacturing process, the filled bags are quickly frozen in the ---(b)(4)--- freezers. The freezer is shared with other products.

The submission does not contain description qualification, validation information and change over procedures. This freezer was reviewed during PLI, and EIR except is copied in italic:

For OAB:

6. -(b)(4)- Freezer

***(NK)** During observation of the freezing process on 24 July 2012, I inquired about its validation. I was provided with a summary of qualification 30-1416-V301 for deep freezing [Ex. NK-6]. The study was designed to provide documented evidence that ---(b)(4)--- freezers, ----------(b)(4)----------, were capable of freezing maximally loaded -----(b)(4)---- filled bags) to ------(b)(4)----- temperature of (b)(4) within (b)(4). --------(b)(4)--------- was conducted in each freezer. ----(b)(4)---- were placed in bags located in the ----------(b)(4)----------. The time recorded to reach (b)(4) ranged from ----------(b)(4)----------. All bags reached a ----(b)(4)----- temperature of (b)(4) by the end of the (b)(4) freezing time*

For OPG:

The ----(b)(4)---- freezer in Room (b)(4) has (b)(4) identical freezers made by ----------(b)(4)----------. Validations were conducted for all (b)(4) freezers using standard plasma bags containing plasma. Performance Qualification report for the (b)(4) freezer (080RPQ00026.105) issued in May 2000 was reviewed during the inspection. Temperature distribution in the load was studied with ----------(b)(4)----------, hot and cold spots were identified. The required temperature of (b)(4) as required could be reached. The report demonstrated the capability to reach the required temperatures in bags filled with plasma when they were packed in cartons and positioned in the freezer using standard freezing cycle. During routine productions, temperature sensors are calibrated every ---(b)(4)---. Revalidation occurs when ----------(b)(4)---------- following a review by validation review committee.

AUTOCLAVE

Autoclaves are used for sanitization/sterilization of ----------(b)(4)----------.

The submission does not contain any detailed information on these equipments. These equipments were covered extensively during PLI and see EIR excerpt copied below:

Autoclave at OPG

*(**JH**)During the walk through of the facility, I saw (b)(4) autoclave (----------(b)(4)----------) in the Class (b)(4) area in the --------(b)(4)-------. The autoclave is used to sanitize ----------(b)(4)---------- parts used for OctaplasLG production. Summary report for IQ/OQ/PQ was provided (Doc. No. 060VFK036), including ------(b)(4)------ and ------(b)(4)------ validations. Revalidation of the autoclave is conducted (b)(4). Parts used for ----------(b)(4)---------- are sterilized. Latest revalidation report for the autoclave was provided (Doc No. 080RPQ1153.001). -------(b)(6)-------- went over the validation of the autoclave and PM program. ----(b)(4)---------- load studies were performed to evaluate the minimum load (---(b)(4)---) and various standard loads ((b)(4) studies) conditions, and the load -----(b)(4)------ are detailed in the report. The acceptance criteria are as follows:*

(b)(4)

1 page redacted (b)(4)

(b)(4)

----------(b)(4)----------.

All results for temperature, inactivation of the bioindicators and pressure met the acceptance criteria.

-------(b)(6)------- went over the maintenance plan (Doc. No. 060WPL007_03_steam sterilizer_engl) for the autoclave. The plan listed routine PM work/check, responsible work unit and intervals. (b)(4) preventative maintenance is done by vender. For routine maintenance, the electronic system -(b)(4)- will issue PM work schedule automatically.

I reviewed the user SOP and current log book for the autoclave, and no irregularities were noted. I noticed there is no procedure in SOP and log book to ensure (b)(4) filter change is done properly, and the firm agreed to address this.

Autoclave at OAB

(JH)*On July 25, 2012, I interviewed -------(b)(6)------- with regard the autoclave --(b)(4)-- used for Octaplas production, and collected validation report (OAB 07-16; 30-1416-V202) for the autoclave. The validation report contained studies of ----------(b)(4)----------, and tests results. (b)(4) runs with maximum load and (b)(4) with minimum load were conducted. The maximum loads contained ----------(b)(4)----------. parts, and the minimum load contained ----------:*

(b)(4)

All results for temperature, inactivation of the bio-indicators and pressure met the acceptance criteria.

I have also reviewed the maintenance plan for the autoclave. It describes minimum maintenance responsibility, strategy intervals (b)(4) preventative maintenance is done by vender.

I also reviewed the logbook for the autoclave and no objective conditions were noted.

SHIPPING [Module 3.2.P.3.5]
OctaplasLG™ bags manufactured in Europe (at Octapharma PPGmbH, Vienna, Austria and at Octapharma AB, Stockholm, Sweden) will be shipped to the USA by validated -----(b)(4)---- and -------(b)(4)------- Containers. A simulated shipment validation for OctaplasLG™ is included in the submission which reported (b)(4) simulated test runs based on the worst case scenarios conducted in OAB site in Sweden. ----------(b)(4)---------- transport vessels were tested with (b)(4) inside temperature logger and (b)(4) outside temperature logger. Inside
----

----------(b)(4)----------

----------.

(b)(4)

During our inspections, Octapharma provided actual shipping data of OctaplasLG™ to ----------(b)(4)----. No deviation was reported, and more detailed information is covered in the EIR.

On October 9, 2012, Octapharma submitted amendment #27 in which Octapharma agrees to submit a shipping study for Octaplas™ from production facilities in Vienna, Austria and Stockholm, Sweden to US distribution site.

UTILITIES
HVAC [Module 3.2.A.1.5]
OAB site:
The air to the OctaplasLG™ production area is provided by (b)(4) Air Handling Units (AHU), including ----(b)(4)---------- AHUs and ---(b)(4)--- AHUs. ----------(b)(4)---------- areas are supplied by different AHUs which provide for the strict separation of the air. For grade -(b)(4)- area, ----------(b)(4)-- air supply is used. Grade --(b)(4)-- have --------(b)(4)--------- in AHU with ----------(b)(4)---------- is not used in any cleanroom ventilation system. The air is ----------(b)(4)---------- for all classified rooms grade ----(b)(4)---- located in the ---(b)(4)--- of the cleanrooms.

Schematic HVAC for OctaplasLG™ production area is provided in the submission and the individual air handling unit is shown in the table below:

(b)(4)

The classification of the clean room area is based on the current ---(b)(4)--- guidelines as defined in the --(b)(4)-- regulations. Assignment of Products / Processes to the Appropriate Environment, and Pressure difference between clean room classifications are listed in the table below:

(b)(4)

Air flow patterns in room grade (b)(4) are qualified and (b)(4) studies were conducted. IQ/OQ/PQ were performed for all Grade (b)(4) after the production building was revamped and the line was finalized 2009. The clean room validation IQ/OQ/PQ-reports were approved in 2010.

IQ/Commissioning tests are as described in the table below:

(b)(4)

Summary of OQ tests are listed in the table below:

(b)(4)

Maintenance of HVAC system

All equipment within Octapharma AB is listed in a maintenance data system. Working order for preventive maintenance and calibration are automatically generated by the software. Each AHU is checked and serviced according to a regular maintenance schedule. (b)(4) air filters are changed -(b)(4)- and (b)(4) air filters are changed --(b)(4)--. The integrity of the -(b)(4)- filters in ---(b)(4)---

2 pages redacted (b)(4)

(b)(4)

----------(b)(4)----------

----------.

OPG site

The air to the OctaplasLG™ production area is provided by (b)(4) Air Handling Units (AHU). ----------(b)(4)---- areas are supplied by different AHUs which provide for the strict separation of the air. The air is ----------(b)(4)----------. The air is ----------(b)(4)---------- for all classified rooms grade ---(b)(4)--- located in the --(b)(4)-- of the cleanrooms.

The air pressure is regulated by air pressure --------(b)(4)--------. Air flow patterns in room grade (b)(4) are qualified and studied with (b)(4). The HVAC system was installed in 1992 and revamped in 1998. In 2006 a new monitoring system was implemented and IQ/OQ for this system were performed and completed successfully in 2006/2007. The last validation of the HVAC system was performed in the course of periodic validation and calibration during the -----(b)(4)------ in 2010.

The classification of the clean room area is based on the current European guidelines as defined in the

3 pages redacted (b)(4)

(b)(4)

----------(b)(4)----------

----------.

WATER SYSTEMS [Module 3.2.A.1.6]

OAB site:

OAB water system for OctaplasLG production consists of a purified water system, and a hot WFI system. The purified water system feeds water to WFI system and to Pure Steam Generator (PSG). The Hot WFI (WFI-(b)(4)-) system feeds water to other PSG, to cold WFI, to buffer preparation and to cleaning of product contact equipments processes.

Purified Water

The specification for OAB Purified Water conforms to -------(b)(4)------- standards. Octapharma reported that IQ/OQ/PQ performed in 2004 met the specifications. Parameters tested during the qualification study of Purified Water included: ----------
----------(b)(4)----------
--------. All tested parameters met the acceptance criteria. The results of qualification proved that the --(b)(4)-- Water System consistently delivers purified water that meets (b)(4) specifications.

Water For Injection (WFI)

The OAB WFI system is composed of ----------(b)(4)----------, each connected to ----------(b)(4)----------. This entire WFI-system was validated October 2002. The OctaplasLG™ Production area was validated in 2009 with installation of new pipes. Parameters tested during performance validation are listed in the table below:

(b)(4)

(b)(4)

OAB WFI conforms to -----(b)(4)------ standards. Parameters tested during the (b)(4) validation of hot WFI included ----------(b)(4)----------. All results met acceptance criteria.

----------(b)(4)----------.

Routine Monitoring

The monitoring specifications and frequency for all water types was included in the submission. No work is performed ----(b)(4)----, thus it is ----------(b)(4)----------. OAB has a written routine monitoring program that defines the actions to be taken when limits are exceeded. WFI monitoring is summarized below:

(b)(4)

Octapharma stated that a review of all monitoring data is performed ---(b)(4)--- by QA to evaluate results. Planned actions are in place for exceeded limits as well as investigation of excursions and follow-up of effectiveness of initiated CAPAs.

For clean steam system, please refer to the EIR excerpt copied below in italic:

6. Clean Steam

***(JH)** I interviewed ----(b)(6)----- (Utility & facility engineer), Christine Bellander (QC manager) and ---(b)(6)----- regarding the validation and the PM of the clean steam system. The clean steam system was validated for use in the ----------(b)(4)----------. The clean steam system conforms to the same specifications as --(b)(4)---. The firm provided SOP 7068-OF, "Sampling frequency & the scope of analyses regarding the WFI and Pure Steam systems", Validation Instruction 4017-OT (IQ/OQ requirements for clean steam), Qualification summary report and facility steam piping diagrams for the clean steam system used for OctaplasLG production in (b)(4) floor of Building (b)(4). Documents contains (b)(4) listed sampling points, sampling frequencies, routing monitoring plan and SOP for major interventions, such as installation of additional sampling points, replacement of heat exchangers or rebuilding of distribution loops.*

I reviewed the Qualification summary report (No. 30-1401-V086) for the clean steam system which documented IQ/OQ/PQ processes of the new clean steam system. There were 4 minor deviations found and they were all addressed and closed.

I reviewed the validation instruction, and the validation requirement for all sampling points which must be tested for the following:

- *----------(b)(4)----------*
- *----------(b)(4)----------*
- *----------(b)(4)----------*

The steam generator is located ------(b)(4)-------- (Sampling points ----------(b)(4)---------- are sampled every ---(b)(4)--- and tests include: ----------(b)(4)----------.

Each of the sampling points in the OctaplasLG production facility are sampled every ----(b)(4)-. The sampling times for each sampling point are distributed evenly over time so that ---(b)(4)---- sampling point is sampled ---(b)(4)---. The following tests are performed: ----------(b)(4)----------.

Minor interventions (e.g. ----------(b)(4)----------) require additional testing for ----------(b)(4)----------. Facility and utility management is responsible for collecting the samples required. QC Starting Materials is responsible for informing the sampling point owner about the outcome.

Major interventions (e.g. ----------(b)(4)----------) require change control followed by qualification. Facility and utility management is responsible for required measurements to be taken.

There is a ---(b)(4)--- QA approval system set up for the clean steam system. ----------(b)(4)---------- is the minimum requirement for use of WFI/pure steam for manufacturing or research purposes. All testing included in the IQ/OQ protocols must be performed and approved. All test results from the process validation sampling must be approved. Decision regarding interim approval must be made by the same functions that authorized the PV protocol, and the outcome must be documented.

----------(b)(4)---------- is required for release of products affected by the PV. Decision regarding interim approval must be made by the same functions that authorized the PV protocol, and the outcome must be documented.

---(b)(4)--- revalidation of the system is conducted according to Instruction 7060-OF. Requalification will be performed if there are any ----------(b)(4)---------- is observed.

No objectionable issue was found.

OPG site:

OPG's water system consists of the ----(b)(4)---- water and WFI -----(b)(4)-----

The ----(b)(4)---- include: --------(b)(4)---------- (Cleaning/rinsing of equipment during ----------(b)(4)----------; manual cleaning and ----------(b)(4)---------- sterilizer. Last validated in September 2008); ----------(b)(4)----------. Last validated in September 2008); and --(b)(4)-- (Supply of (b)(4) water to distribution system (b)(4)).

The OPG WFI system for OctaplasLG production includes----------(b)(4)---------- supplies WFI to ---(b)(4)--- for distribution where WFI is used for ----------(b)(4)----------.

-----(b)(4)------
OPG (b)(4) Water conforms to ----------(b)(4)----------. IQ/OQ/PQ for the system were initially performed in 2001, and revalidations have been performed in 2004, 2005, 2007 and 2009 when new piping and use points were implemented.

Parameters tested during qualification study of (b)(4) Water included: ----------(b)(4)----------. All tested parameters met the acceptance criteria.
The results of PQ proved that the --(b)(4)-- Water System produces (b)(4) Water of specified quality in a consistent manner. The system consistently delivers water that meets Purified Water, (b)(4) specifications.

Water for Injection (WFI)
The WFI system is composed of ----------(b)(4)----------, each connected to ----------(b)(4)----------. This entire WFI-system was validated October 2002. The ----(b)(4)---- in OctaplasLG™ Production area was validated in 2009 with the installation of new pipes.

OPG WFI conforms to ----------(b)(4)----------. Parameters tested during the validation ----------(b)(4)----------.

Routine monitoring
The monitoring specifications and frequency for monitoring all water types was included in the submission. The firm has a written routine monitoring program that defines the actions to be taken when limits are exceeded. Samples are taken at a selected drawing point (b)(4) for measurement of ------(b)(4)--------. In addition, samples of selected points of the loops are

tested for ----------(b)(4)---------- comprises testing for ----------(b)(4)---------- samples of selected points are tested for ----------(b)(4)----------. WFI monitoring is summarized below:

(b)(4)

*----------(b)(4)----------

The submission notes that a review of all monitoring data is performed ---(b)(4)--- by QA to evaluate results. Planned actions are in place for exceeded limits as well as investigation of excursions and follow-up of effectiveness of initiated CAPAs.

During PLI, we reviewed PQ report for the WFI system, and no objectionable condition observed.

Clean steam system at OPG

Clean steam system was reviewed during PLI, and excerpt from EIR is copied below in italic:

*(**JH**)I interviewed ----------(b)(6)---------- regarding validation and PM of the clean steam system used in manufacturing of OctaplasLG. The clean steam generator (----------(b)(4)----------) is supplied by ---------(b)(4)------- water. The system distribution loop supplies steam to all manufacturing areas that require Clean Steam for ----(b)(4)-----. The clean steam system has been validated for use in the ----------(b)(4)----------. The system conforms to the same specifications as ---(b)(4)---. I was provided with the following documents regarding clean steam:*

- *SOP (001SOP550/01) for routing monitoring of clean steam.*
- *QC Specifications for clean steam*
- *Maintenance SOP for clean steam generator ---(b)(4)---*
- *Master validation plan. Doc. No. 080LIS00007.023*

The tests performed and acceptance limits (---(b)(4)---) are listed in the table below:

(b)(4)

Sampling point for clean steam ----------(b)(4)---------- ----------. The steam generator (-(b)(4)-) has -(b)(4)- maintenance plan that has functional checks, shutdown/restart and cleaning procedures to be conducted for regular maintenance and intervals.

-(b)(4)- revalidation of the system is conducted according to Instruction 080LIS00007.023. Requalification will be performed if there is any ----------(b)(4)---------- or significant --------(b)(4)---------- is observed.

No objectionable issue was found.

COMPUTER SYSTEM [Module3.2.A.1.7]
In the BLA submission, Octapharma listed the computerized systems used in the production of OctplasLG at both OAB and OPG site. The computer systems are categorized into Administrative System and Computer Controlled Manufacturing Processes.

Administrative System
Both sites utilize the same administrative computerized system as outlined below:

----------**(b)(4)**---------- – The (b)(4) database based (b)(4) system systems are supplied by ----------(b)(4)---------- at OPG and by ---------(b)(4)--------- at OAB. (b)(4) monitors the following functions:

- ---------(b)(4)----------
- ----------(b)(4)----------
- ---------(b)(4)----------
- ----------(b)(4)----------
- ---------(b)(4)----------
- ----------(b)(4)----------
- ---------(b)(4)----------

----------**(b)(4)**---------- – Following activities are supported by ---(b)(4)---:

- ----------(b)(4)----------

- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------

Computer Controlled Manufacturing Processes

For both sites, the manufacturing process is manually monitored in general. Certain manufacturing steps are however supported by computerized systems. There are no automated decision-making systems in terms of batch processing.

OAB site automated process control system

OAB Process control system includes: Large Control Systems (LCS), Small Control Systems (SCS), Programmable Logic Controllers (PLC), and Applications subsystems. These systems provide various levels of control and tracking of the production process.

- ----------(b)(4)----------.
- ----------(b)(4)----------.
- ----------(b)(4)----------.
- ----------(b)(4)----------.
- ----------(b)(4)----------

All these systems were installed in 2009 and validated. For each system, the parameters are predefined; password protected and can only be changed by the supervisor. The user starts/stops and supervises the process on the Operator panel.

OPG site computer controlled manufacturing steps

The automated systems used in manufacturing at OPG site can be divided into three categories: remote control systems (RCS), sequence control systems (SCS), and package unit systems (PUS). The computerized systems are as following:

- ----------(b)(4)----------.
- ----------(b)(4)----------.
- ----------(b)(4)----------

Validation of computer systems
Both sites use the same validation approach. The validation of computer systems is based on the ---(b)(4)--- guidelines (----------(b)(4)----------). The responsibilities, the system life cycle, the validation procedure, and the required documents are described in the validation master plan and in SOPs.

Prior to qualification/validation, each component of the computerized system is classified according to the categories defined in -(b)(4)- following internal procedures. According to the classification the extent of the qualification/validation required for the respective software or computerized system is determined.

For legacy systems which have been in use for a long time without major changes and where no detailed functional specifications or design specifications are available, there is an overall assessment of performance (results of PQ, cleaning validation, process validation) of the calibration and maintenance status. Furthermore, the logbook records are reviewed. This assessment is summarized as experience report which substitutes for IQ and OQ.
Changes to computer systems are handled according to SOPs. These procedures state that changes are documented and categorized, and impact assessed before implementation. Changes require authorization from system owner and QA.

In general computer validation is performed as part of the equipment qualification where the software and automation hardware are an integral component. Therefore, starting from OQ, computer system functions are validated together with the mechanical functions of the respective equipment.

Review comment: During PLI, computer system was inspected and no issue was identified.

PREVENTING CROSS CONTAMINATION [Module 3.2.A.1.4]
OctaplasLG productions at both OAB and OPG share production areas and some equipment with other products. Octapharma established procedures to prevent cross contamination.

As production advances through the process, the process material moves from ---(b)(4)--- area to Class ----------(b)(4)---------- for sterile filtration and Class --(b)(4)-- for filling. Access to the production areas is controlled and restricted to authorized persons. The gowning procedures and requirements for personnel hygiene are defined in SOPs. An environmental monitoring program designed for the specific clean room class and criticality of the processes performed therein has been established. Performance of aseptic filling processes is requalified with media fills on ----------(b)(4)----------. Materials flow and waste flow are designed to prevent cross contamination. Room cleaning is done ----------(b)(4)--------- the room for processing. Standard procedures for room cleaning and disinfection, frequency of cleaning, use of detergents and disinfection agents and specifications on the accepted microbial contamination are detailed in respective SOPs of the operating departments. The surface and/or spray disinfectants used are rotated periodically. Different

cleaning and disinfection agents are used per written procedures, rotated, and effectiveness demonstrated in validation studies.

All equipments used in Octaplas™ manufacture are cleaned ---(b)(4)--- as per written SOPs. Standard procedures for cleaning and disinfection, frequency of cleaning and disinfection of equipment, use of detergents and disinfection agents and specifications on the accepted microbial contamination are detailed in respective SOPs of the operating departments. All shared product contact equipments are cleaned and sanitized with validated ---(b)(4)--- procedures. Dedicated equipments are used for Octaplas™ US production that are ---(b)(4)--- washed, such as ----------(b)(4)----------.

Routine training programs have been instituted for all personnel with their intended duties. All personnel that directly participate in the critical processing zones during the set-up and filling of sterile products have to take part in a media fill that meets the requirements, at least --(b)(4)--. Transfer of personnel between classified areas is possible only through ------(b)(4)-------- where the staff ----------(b)(4)---------- according to the gowning procedures outlined in the current SOPs.

STERILITY TEST [Module 3.2.P.5.3]
OctaplasLG is s sterile product, and the sterility result is required in the final release testing. The following sterility test validation reports were provided in the submission:

- Determination of Test for Sterility by -------(b)(4)--------- on OCTAPLAS / ----------(b)(4)-------- (Doc. No. 001VAL106 FC 93x 95x / 00)
- Determination of Test for Sterility by --------(b)(4)---------- with ----------(b)(4)---------- (CC 04/12))(Doc. No. 001VAL106 FC of all products Suppl.1)

The test was conducted according to SOP 001SOP106/02. The Octaplas® lot ----(b)(4)--- was used for the study, and the following microorganisms were used in the study:

- ----------(b)(4)----------
- ----------*(b)(4)*----------
- ----------(b)(4)----------
- ----------*(b)(4)*----------
- ----------*(b)(4)*----------
- ----------*(b)(4)*----------

Media and solutions:

- Soybean Casein Digest Broth, CSB (----------(b)(4)----------)
- Thioglycollate Broth with ---(b)(4)---, THIO (----------(b)(4)----------)
- ----------(b)(4)----------

Those studies have demonstrated that the tests for “Sterility” by ------(b)(4)--------- with ----------(b)(4)---------- on Octiplas, --(b)(4)-- and ALBUMIN25% were satisfactory

according to ----------(b)(4)----------. The study demonstrated that Octaplas is compatable to the tested microorganisms, and clearly visible growth of all the test micro-organisms was obtained after incubation, visually comparable to that of the positive controls. It was concluded the test for sterility of OCTAPLAS / ----(b)(4)---- is valid and is suitable for use in routine tests**.**

PYROGEN TEST [Module 3.2.P.5.3]
OctaplasLG is a pyrogen free product. Pyrogen test is required in the final release testing. Pyrogen tests of OctaplasLG samples from both OAB and OPG are performed by the company ----------(b)(4)----------. Test procedures and acceptance criteria are outlined. PQ of the test method was successfully performed. This is reviewed by DBSQC.

2 PAGES REDACTED (B)(4)

MATERIAL FLOW [Module 3.2.A.1]
The firm provided diagrams to show detailed material flow floor plans for both sites in section 3.2.A.1. Materials are separated for production and aseptic processing steps. ---(b)(4)--- are washed, dried and depyrogenated by sterilizing in a dry heat tunnel before being transported into the filling room. Material flow appears adequate for the facility.

PERSONNEL FLOW [Module 3.2.A.1]
Personnel flow is described in section 3.2.A.1 for both sites. Entrance to the facility is made though -------(b)(4)------- and require code cards for access. The firm provided detailed personnel flow floor plans. Different colored gowns are used for different production areas and room classifications to identify personnel working in the different production areas. Personnel flow and gowning appears adequate for the facility.

WASTE FLOW [Module 3.2.A.1]
The firm provided detailed waste flow floor plan for both sites in section 3.2.A.1 . Production waste leaves the facility through the ------(b)(4)-----. Waste flow appears adequate for the facility.

ENVIRONMENTAL ANALYSIS [Module 1.12.14]
Octapharma Pharmazeutika Produktionsges.m.b.H. claims categorical exclusion for Octaplas™ as outlined in 21 CFR Part 25.31 (c) documented in a separate CE memo

REVIEW OF AMENDMENTS

A teleconference was requested by DMPQ and was held on 27-Mar-2012. DMPQ requested general information regarding facilities and equipments sharing for OctaplasLG™ with other US licensed products at OPG and OAB sites. Octapharama submitted amendment #1 on 6-Apr-2012 and confirmed that the production lines (area/equipment) for OctaplasLG™ are not shared with any other FDA licensed US product at both OAB and OPG sites. The record of the telecon is in EDR.

A combined Information request with questions from DMPQ and product reviewers was sent to Octapharma on 25-Apr-2012. Between 15-May-2012 and 17 Sep 2012, Octapharma submitted amendment #2, #3, #9, #14, #18, #19 and #21 to address DMPQ related questions. Amendment #24 contained responses from Octapharma to 483s issued to OAB and OPG during PLI, and the review of amendment #24 is covered in a separate memo.

A telecon was held on October 4, 2012. DMPQ reviewer conveyed concerns with Octapharma's change of ----------(b)(4)----------. Octapharma responded on October 5, 2012 in email and on October 9, 2012 in amendment 27 agreed to change the acceptance limit for ----------(b)(4)---------- which is the same as -------(b)(4)---------.

An IR for shipping study PMC was communicated to the firm on October 5, 2012, and Octapharma agreed to the PMC in amendment 27 received on October 9, 2012.

AMENDMENT #001

Dated 6-Apr-2012 (response to DMPQ telecon of 27-Mar-2012)

Question 1:

Which other US licensed products are manufactured in the same area and share the same equipment with octaplasLG? Please provide a detailed site by site comparison in tabular form listing manufacturing step, shared equipment, shared rooms by room number, and the respective US licensed product (i.e. ----------(b)(4)----------).

Response to Question 1:

Octapharma reported that OctplasLG does not share areas and equipment with other US licensed products. At **OPG**, Octaplas® ----(b)(4)----- are also produced. At **OAB,** only Octaplas® is produced.

Response was not adequate in addressing our question. Octapharma provided more detailed answers to the question in amendment #2 and #3.

Question 2:

Please provide a site by site comparison between the manufacturing of OctaplasLG™ at OPG Vienna and OAB Stockholm.

Please provide a site by site comparison in tabular form listing room numbers, names, manufacturing step, major equipment, and equipment differences.

Response to Question 2:
Octapharma reported that there are no differences in the manufacturing process at OPG Vienna and OAB Stockholm, but there are differences between the production lines.
OPG Vienna has been routinely manufacturing *Octaplas* since 1992 and OctaplasLG™ since 2009. OAB Stockholm has a new production line that was implemented and fully validated for OctaplasLG™ in 2011. Equipment at OAB Stockholm is qualified to process both 390 kg and (b)(4) starting amount of plasma in contrast to 390 kg only at OPG Vienna. Current BLA requests market approval for the batch size of 390 kg only. Differences in major equipment between manufacturing sites were provided as well as major equipment comparison tables.

Response was adequate. The information provided is contained in this review memorandum in the Major Equipment section.

AMENDMENT #002 dated 15-May-2012
AMENDMENT #003, dated 24-May-2012
Response to IR of April 25, 2012

Amendment #2 only addressed #1 and #2 IR questions, and the same responses were also included in amendment #3

Question 1
Please provide a detailed list of other products that share the same manufacturing areas/rooms with OctaplasLG® (US) at both OPG and OAB sites. Octapharma provided a list of products that share the same general area with OctaplasLG® (US) manufacturing, but not specific rooms shared during each step of the manufacturing process.

Response to Question 1
The following products share the same production area at the manufacturing site **OPG**:

----------*(b)(4)*----------
----------.

In **OAB,** -----(b)(4)----- share the same production line with OctaplasLG™.

A listing of manufacturing steps according to Method of Preparation (MOP), room numbers / names at OAB and OPG, and other products manufactured in the respective rooms/areas was provided. The other products that share the same area with OctaplasLG are the ----------
-(b)(4)--, and all product contact equipment are either -(b)(4)- cleaned or dedicated --(b)(4)--, so this does not present concern for contamination.

Response was adequate

Question 2

Please provide a detailed list of product contact equipment, including single-use and reusable, dedicated and shared for manufacturing of OctaplasLG™. For each piece of shared equipment, please list all products that share that piece of equipment with OctaplasLG™ (US) at both OPG and OAB sites. [The tables in 3.2.A.1.3.1-Preparation, Cleaning and Sterilization of Equipment only indicated if the equipment is shared, but did not identify which products shared each piece of equipment.]

Response to Question 2

Firm reported OctaplasLG™ manufactured from non-US plasma shares the same equipment and rooms with OctaplasLG™ produced from US plasma. The gel for the (b)(4) column will be dedicated for US market, only. The gel for the ----------(b)(4)----------.

List of product contact equipment, the respective usage ------(b)(4)---------, the dedication status, and other products the equipment that shared with was provided. A correction noting ---(b)(4)--- LG columns are used at both manufacturing sites instead of (b)(4) column in the original submission was also included.

DMPQ has reservation regarding sharing any equipment that can't be CIP/SIP cleaned, and that applies to sharing (b)(4) columns with with non-US plasma. Upon conclusion of PLI, Octapharma agreed to use dedicated (b)(4) columns for US Octaplas™.

Response was adequate. The tables provided within the body of this review memorandum are the tables that were provided within this response.

Question 3

Please provide the following regarding automatic cleaning and sanitization for stainless steel vessels:

a. *Rationale for the selected cleaning procedures which addresses their effectiveness for the residual products to be removed.*
b. *Validation report, including SOP number, describing the cleaning validation procedures for removal of product residues and cleaning agents. The report should identify the sampling and analytical methods used and address their sensitivities and specificities, and revalidation intervals.*
c. *Specify sterile hold time for cleaned equipment and intervals when CIP/SIP needs to be performed again.*
d. *Please justify why TOC, bioburden and endotoxin are not tested during cleaning procedures to monitor their effectiveness.*

Response to Question 3

a. Firm provided defined cleaning cycle, and stated the cleaning process was validated using a defined currently validated cleaning method.

b. Two summary PQ reports regarding cleaning validation activities for OctaplasLG™ were included. The review of these summary reports is contained in the body of this review memorandum.
OPG: *Report 080RPQ12202.000: "Summary of Validation Reports concerning Cleaning / Sanitation / Sterilization / Depyrogenisation for equipment used during OctaplasLG™ processing"*,

OAB: *Report OC12-0157: "Summary of Validation Reports concerning Cleaning and Sanitization of Stainless Steel Vessels used in the OctaplasLG™ Production at Octapharma AB, Stockholm"*.

c. The defined clean hold times of (b)(4) at OPG and -(b)(4)- at OAB for automatically cleaned stainless steel vessels for the production of OctaplasLG™ were demonstrated in course of the respective cleaning validation. This was
---

----------(b)(4)----------

----------:

(b)(4)

d. ---

----------(b)(4)----------

----------.

Responses were adequate.

Question 4

Regarding manual cleaning:

a. *Please justify the omission of surface swab sampling and testing for bioburden or endotoxin after cleaning. Please reference the relevant SOP on how monitoring is performed and the acceptance parameters.*
b. *Please explain why different detergents (------(b)(4)------ detergent at OPG and ----------(b)(4)---------- detergent at OAB) are used at different sites for manual cleaning of minor equipment.*

Response to Question 4

a. At both sites, the ----------(b)(4)---------- had been performed during cleaning validation of manually cleaned equipment. For small equipment, the ------(b)(4)------ whenever possible. For areas that are hard to reach and ----------(b)(4)---------- was used.

   At OPG, the sampling was performed according to SOP 087SOP006 "Cleaning Validation; Procedure at manually cleaned equipment".

   At OAB the sampling was performed according to SOP 7026-OFS "Performance Qualification (PQ) of manual cleaning" and SOP 7028-OFS "Chemical control of residues and surface sampling".

   ----------**(b)(4)**----------

   (b)(4)

   (b)(4)

At OPG, monitoring after manual cleaning during routine production is performed according to SOP 087SOP004 "Cleaning Validation Strategy". Monitoring -(b)(4)- during routine production is performed ----------(b)(4)---------- and analysis of ----------(b)(4)---------- according to SOP 4007-OP "-----(b)(4)----- of vessels Octaplas". In addition, (b)(4) samples are taken ------(b)(4)------. Revalidation of the automatic cleaning process shall also be performed if the ----------(b)(4)----------.

At OAB, the implementation of a SOP for monitoring for manual cleaning during routine production of OctaplasLG™ is on going and will be finalized in august 2012.

b. OAB has developed and validated its own manual cleaning concept prior to its acquisition by Octapharma, which is still in place. Therefore, two different validated detergents at OPG and OAB are in use.

Responses were adequate.

Question 5

The submission does not contain information regarding if any --(b)(4)-- or chromatography units are used for the manufacturing of the product. Please provide a description of the equipment, the dates for IQ/OQ/PQ, and validation report.

Response to Question 5

Firm reported that both sites have used ---------(b)(4)---------- during the manufacture of OctaplasLG. For C-18 chromatography and LG chromatography at OPG, ----------(b)(4)---------- is used instead of a -------(b)(4)------- (as at OAB) to apply the product onto the column. The chromatography units are assembled manually and connected to the respective ----------(b)(4)----------. Column loading, washing, and elution is monitored by ------(b)(4)----- and recorded.

Response was adequate

Question 6

Please provide the following for the C-18 ---(b)(4)--- column:

a. The construction of the column including materials and specifications.

b. ----------(b)(4)----------. Please justify the omission of TOC and bioburden tests and the lack of ----------(b)(4)----------. Please provide relevant validation study reports.

c. Sterile hold/storage time and requalification interval with supportive data to justify the set times.

d. Cleaning procedures and frequency of replacement for accessory parts, such as gaskets and flow plates.
e. ----------(b)(4)----------.
f. Criteria for switching between control of column loading procedure by ----------(b)(4)---------- or validation of their interchangeability
g. Operational temperature
h. Elution conditions and criteria for peak collection
i. Representative elution profile
j. Elution conditions and criteria for peak collection
j. k. Representative elution profile

Response to Question 6

a. For C-18 chromatography ----------(b)(4)----------. The construction of the C-18 columns used was presented in picture diagrams. Materials and dimensions of components of the C-18 columns were presented. The response was adequate.

b. Conductivity is not measured since ----------(b)(4)---------- instead, and is considered to give adequate information. TOC testing is not possible due to the presence of ----------(b)(4)---------- were tested during validation, and that justified only --------(b)(4)---------- are tested during routine manufacturing process. The response was adequate.

c. Summary cleaning validation reports for the C-18 columns At OPG and OAB were provided:
   b. OPG: *Report 087RPQ11370.105 "Cleaning and Regeneration of the C-18 column in the OctaplasLG™ production*".
   c. OAB: *Report OC12-0180: "PQ Report, Validation of cleaning and regeneration of the C18 column --(b)(4)-- used in the OctaplasLG™ Production at Octapharma AB, Stockholm."*

The reports provided sufficient data regarding hold time and revalidation interval. The response was adequate.

d. The acceptance criterion at both sites for ----------(b)(4)---------- and corresponds to the (b)(4) specifications according to the (b)(4). Since the defined acceptance criteria are in accordance to the (b)(4) specification, no quantitative assessment was performed.

We do not agree with non quantitative assessment of the ----------(b)(4)--------, and Octapharma later agreed to report the data quantitatively.

e. Clean hold/storage times are not defined at the time of the response. For both sites, qualification of the clean hold time for the C-18 column is ----------(b)(4)----------.

Although there is no validated defined clean hold time available, because the column is tested for ----------(b)(4)----------, the process is still well controlled. The response was adequate.

f. For both sites, frequency of replacement of accessory parts is carried out as follows: ----------(b)(4)----------.

We have concerns regarding shared parts in column for US and non-US plasmas. Octapharma later agreed to use dedicated columns for US Octaplas™ as reviewed in OAB 483 item #1.

g. Analysis of historic data from (b)(4) Octaplas/ OctaplasLG batches manufactured from January 2011 to April 2012 showed that ----------(b)(4)---------- had a range comparable to the validation runs. So, accordingly the limit for ----------(b)(4)----------.

Response was adequate.

Response to h, I, j and k are reviewed by product office.

Question 7

Please provide the following for prion removal LG chromatography column:

a. Specification of the ---(b)(4)--- column and the ------(b)(4)-------- column, including construction materials and dimensions.
b. Cleaning validation and routine cleaning for the column. Please include dirty hold and clean hold time and studies performed to support these times.
c. Qualification of the column
d. Justification for the omission of ----------(b)(4)---------- tests
e. Quantitative assessment of ---(b)(4)--- with adequately justified acceptance criteria
f. Cleaning procedures and frequency of replacement for accessory parts, such as gaskets and flow plates and supportive data to justify the frequency
g. Explanation for why two different procedures are used during ---------(b)(4)---------- at OPG site in Vienna ----------(b)(4)-----

---------- *and at OAB site in Stockholm* ----------*(b)(4)*----------.

h. Operational temperature
i. Elution conditions and criteria for peak collection
j. Representative elution profile

Response to Question 7

a. ---(b)(4)--- columns are not used at OAB and OPG. For LG chromatography ----------(b)(4)--- columns identical in construction are used at OPG and (b)(4) used at OAB. The construction of the columns used is presented in picture diagrams. Materials and dimensions of components of the columns are presented.

Response was adequate.

b. Report regarding cleaning validation of the LG chromatography column equipment including data justifying a dirty hold time for -----(b)(4)---- is provided: *Report 087RPQ10275.000: Equipment family ------(b)(4)------*. Qualification of the clean hold time for the LG chromatography column is ongoing.

Although there is no validated defined clean hold time available, because the column is tested for ----------(b)(4)----------, the process is still well controlled. The response was adequate. A review of the cleaning validation is contained within the body of this review memorandum in the LG column section.

c. The -(b)(4)- chromatography columns intend to be used for LG have been qualified retroactively according to the "---(b)(4)--- qualification" procedure in May 2009, qualification activities have been summarized retrospectively in qualification report: 060VFK028 ---(b)(4)--- Chromatography Columns.

Response was adequate.

d. Firm stated that ---(b)(4)--- testing is performed on ------(b)(4)-------. But not performed on ----------(b)(4)----------, since it's a validated cleaning process, and measuring of -----(b)(4)------ is sufficient to demonstrate the cleanliness of the column.

Response was adequate.

e. At both sites, the acceptance criterion for ----------(b)(4)---------- which corresponds to the (b)(4) specifications according to the (b)(4).

We do not agree with the non quantitative assessment of --(b)(4)--- result, and Octapharma later agreed to report the test results quantitatively.

f. LG columns are ----------(b)(4)----------. No preventive replacement of accessory parts is performed, since all parts like ----------(b)(4)--------- are inspected prior to packing of the respective column. Damaged parts are replaced immediately. Maintenance is documented in the respective column logbooks. ----------(b)(4)----------. Both sites use the same procedures for ----------(b)(4)----------. Octapharma reported that by mistake wrong information was provided in Module 3.2.A.3.1.3 for OPG in the original BLA , and they provided the corrected information (updated Module 3.2.A.3.1.3 section for OPG).

As with the C-18 column, we have concerns regarding shared parts in column for US and non-US plasmas. Octapharma later agreed to use dedicated columns for US Octaplas™.

g. Both sites use the same procedures for ----------(b)(4)----------. In Module 3.2.A.3.1.3 for OPG in the original BLA mistakenly wrong information is given. Updated and correct Module 3.2.A.3.1.3 section for OPG.was provided.

Response was adequate.

Responses to h, I and j are reviewed by product office.

Question 8

Please indicate where in the submission the specification and validation of the filters used in the following steps in the manufacturing process can be found or if not included in the submission, please provide a description of the filtration processes as well as specifications and validation data for filters used in production:

a. 1 µm membrane filters used after pooling of the thawed plasma and before S/D treatment in Step 2 of the manufacturing process for removal of cells, cell fragments and aggregates.
b. ----------(b)(4)---------- filters used to clear up the aqueous phase after S/D treatment in Step 3 of the manufacturing process.
c. The 0.45 µm and 0.2 µm filters used in the final sterile filtration step.

Response to Question 8

Filter specification reports and validation reports were provided for all the filters, including a sterile filtration report 057RAE012-00 for the 0.2 µm filter. .

This is reviewed in details in the filter validation section of the review memo. Responses to a, b and c were adequate

Question 9

Regarding filling machines:

a. *Please provide a description of the filling machines used in manufacturing of OctaplasLG® (US), the dates for IQ/OQ/PQ, the acceptance criteria for PQ, a summary of the test results, and a summary of any deviations (if deviations occurred, a summary of the investigation and resolution)*
b. *Please provide changeover procedures, since they are shared equipment with non-US OctaplasLG®.*

Response to Question 9

a. Qualification reports for OAB and OPG filling lines were provided:
   - "Installation and Operation Qualification of Filling Machine used in the OctaplasLG® Production at Octapharma AB, Stockholm" (Report No. OC12-0161). 2012
   - "Final report of the installation and operational qualification of the filling machine ---------(b)(4)----------" (Doc. No. 060RAE010). 2005

   ----------(b)(4)----------:
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----------(b)(4)----------
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(b)(4)

Response was adequate.

b. The changeover procedures for OPG and OAB were provided in detail the response. Final report 060RAE010 for retrospective qualification of OPG filling line and Report OC12-0161 “Installation and Operation Qualification of Filling Machine used in the OctaplasLG™ Production at Octapharma AB, Stockholm” are included in the response.

For OAB, the changeover procedures are as follows:

- -----(b)(4)-----:
  - ----------(b)(4)----------
  - ----------(b)(4)----------
  - ----------(b)(4)----------
- ----------(b)(4)----------
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Validated cleaning and change over procedures are provided in the reports for both sites as described above. The responses were adequate.

Question 10

Regarding Container closure:

a. The submission stated that --(b)(4)-- of plasma bags (----------(b)(4)----------) are used for OctaplasLG® (US). Please clarify if (b)(4) bags are qualified and used ----(b)(4)---- at both facilities. Please clarify if these bags have been submitted to FDA and reviewed as part of other submissions. Please provide the STN and approval date if they have been. You have provided a Letter of Authorization to reference ----------(b)(4)---------- pertaining to the plasticized polyvinyl chloride material used by ---(b)(4)--- to manufacture their plasma bags; however, there is no such reference covering manufacture and control of --------(b)(4)------- plasma bags. Alternatively you may provide complete information regarding the safety and performance of each --(b)(4)-- plasma bag to include, but, not be limited to: extractables characterization, leachables testing, toxicity testing and performance as an environmental barrier e.g., to oxidation and light (in addition to -----(b)(4)------- already submitted).

b. Please clarify if ---(b)(4)--- have been used in your CCIT and stability study.

c. Please explain why ----------(b)(4)---------- for CCIT long term stability study were not conducted under pressure.

Response to Question 10

a. ----------(b)(4)----------) have not been submitted to FDA previously. The suitability of using the submitted plasma bags for OctaplasLG™ is proven by the Container Closure Integrity Test Reports and the respective stability reports. The --(b)(4)-- bag is used for Octaplas® in the EU since the first registration in Germany in 1989. The --(b)(4)-- bag is approved in the EU since 2010. The bags are qualified according to ---(b)(4)---------- can be used -------(b)(4)------ at both sites.

b. The submitted CCTI report at OAB covers --(b)(4)-- of plasma bags and the CCTI report at OPG covers ---(b)(4)--- bags only.

c. ----------

----------(b)(4)----------

---.

----------(b)(4)----------

---.

Study Report Container and Closure Integrity Testing ----------(b)(4)----------, study no.09P022, 24 months stability data for OPG was included in the response.

Responses were adequate.

Question 11 to 19 are reviewed by product office.

AMENDMENT #011, dated 13 Aug 2012
In the BLA submission, only simulated shipping study data was presented. During PLI, Octapharma was asked to provide actual shipping data to support their shipping validation. In this amendment, Octapharma provided shipping validation reports for two actual shipping studies with finished S/D plasma from OPG to ------(b)(4)-------. In the --(b)(4)-- study, (b)(4) shipments covering winter and summer conditions from OPG to ---(b)(4)--- were evaluated. In the ---(b)(4)--- study, ----(b)(4)---- of S/D plasma from OPG to ----------(b)(4)--------- was evaluated. In both studies, no deviations were found based on the temperature limit of ≤ -18°C with standard shipping practice..

The shipments to --------(b)(4)---------- resemble similar US shipment in terms of duration and temperature for the same product.

Response was adequate.

AMENDMENT #024, dated 24 Sep 2012
Response to 483s for OAB and OPG. Please see DMPQ 483 response review memo for this BLA.

AMENDMENT #27, dated 9-Oct-2012
Octapharma agreed to the shipping study PMC to submit a shipping study for Octaplas(TM) from production facilities in Vienna, Austria and Stockholm, Sweden to US distribution site by October 22, 2013 as a PMC final report to CBER/OCBQ/DMPQ. DMPQ management decided the PMC is not necessary, and it was removed.

Octapharma harmonized ----------(b)(4)----------, and updated all batch records. Octapharma made the change after we objected the change they proposed in amendment #21 dated 17-Sep-2012 for ----------(b)(4)----------. We have no objection to the ----(b)(4)---- limit which is the same as ------(b)(4)--------.

Responses were adequate.